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13. ABSTRACT ***(Maximum 200 Words)***

Eighty-five hereditary breast ovarian cancer (HBOC) families are identified as having a BRCA1 or BRCA2 germline mutation. Five hundred and thirty eligible individuals were identified for the study. Three hundred and eighty-eight of these individuals provided permission to obtain slides and blocks on their breast cancer. We were not able to obtain 103 of these cases due to the slides and blocks being destroyed or the hospital did not respond to our requests. Slides and blocks have been collected on two hundred and eighty-five cases. Sixteen of these cases were ascertained from Dr. Narod's center in Toronto, Canada. Two-hundred and seventeen are carriers of a BRCA1 mutation and 68 are BRCA2 carriers. Pathologic analysis has been completed on 187 cases, leaving 98 cases pending analysis. H&E slides and DNA flow cytometry were completed for 280 cases. Ninety cases have been evaluated for estrogen receptor (ER), progesterone receptor (PR), and c-erbB-2. Histopathological analysis could not be completed this year by Dr. Marcus and Dr. Page, due to staffing conflicts. In summary of last years results: when compared with non-hereditary breast cancers (HBC), BRCA2 HBCs appear to be more similar to usual breast carcinomas. BRCA1 HBC appears to be the deviant phenotype.

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INTRODUCTION

Highly penetrant inherited breast cancer susceptibility increases substantially in the presence of a BRCA1 or BRCA2 cancer mutation. Each gene serves complex functions in the normal cell that maintains genome integrity thereby preventing the development of breast cancer. More specifically, the wild form of BRCA1 suppresses the proliferation of breast cancer cells. In contrast, the production of characteristic tumor phenotypes in breast tissue can potentially lead to the identification of a constitutive BRCA1 and BRCA2 germline mutation. Highlighting these phenotypic changes will promote an increased understanding of the etiology, pathogenesis, and survival of breast cancer patients who are part of BRCA1 or BRCA2 mutation positive families. It is hopeful that these findings will lead to the control of breast cancer; thereby saving thousands of lives a year.

BODY

To date, eighty-five Hereditary Breast Ovarian Cancer (HBOC) families from the Hereditary Cancer Institute at Creighton University have been identified as having either a BRCA1 or BRCA2 mutation and are eligible for ascertaining subjects for this study. Sixty-eight of these 85 HBOC families carry a BRCA1 mutation and 17 carry a BRCA2 mutation. In addition, 16 cases have been ascertained from Dr. Steven Narod's center at the Women's College Hospital in Toronto, Canada. Eleven of these cases are BRCA1 mutation carriers and 5 are BRCA2 mutation carriers.

The addition of one-hundred and eighty-six cases have been identified as eligible for this study making a total of 530 eligible cases. Please refer to Table 1 for the status of each of these cases. Informed consents and permission forms to release clinical data, slides, and tissue blocks were sent to subjects and to the legal next of kin of deceased subjects. To date, 388 informed consents have been signed and returned to Creighton University. One hundred and forty-eight subjects have completed risk factor questionnaires, which have been forwarded to Dr. Steven Narod's center for data entry and assessment of survival parameters. This information will be used in correlation with the subject's breast cancer staging classification and phenotypic characteristics identified by Drs. Joseph Marcus and David Page.

Three hundred and eighty-eight requests for slides and tissue blocks were sent to the appropriate treating hospital once a signed permission form was received from the subject or the legal next of kin. Of the 388 requests sent, 31 of these requests were not answered by the hospital despite repeated requests and follow-up telephone calls to the pathology department. Unfortunately, we were not able to obtain the slides and tissue blocks on 72 cases due to the institution reporting them as being destroyed, missing, or not available. For many hospitals it is a routine to destroy stored slides and tissue blocks after a set number of years.

Over the past year we have almost doubled the number of case samples and tissue blocks that will be used for the final analysis. We now have 217 BRCA1 cases and 68 BRCA2 cases. Please refer to Table 2 for the status of ascertained slides and tissue blocks. After a random number was assigned to the ascertained case an H&E stained slide and corresponding tissue blocks were sent to Dr. Norman Lehman in the Department of Pathology at Creighton

University. At that point Dr. Lehman would select the best tissue block to cut a slide from for Drs. Marcus and Page analysis. Once slides were selected, additional slides were cut from the accompanying blocks for the study and archived. Dr. Lehman also ensures the completion of DNA flow cytometry on each case and performs the hormone receptor tests: estrogen receptor (ER), progesterone receptor (PR) and c-erbB-2 on each usable case. Immunohistochemical assays for ER, PR, and c-erbB-2 were performed according to manufacturer's protocols on an automated immunostainer (Ventana Medical Systems, Tucson, AZ) using Ventana primary mouse monocloncal antibody clones 6F11, 1A6, and CB11, respectively. Tumors were then classified histologically by two pathologists, Joseph Marcus, MD and David Page, MD, in a double-blind manner, all as before (4-6).

KEY RESEARCH ACCOMPLISHMENTS & REPORTABLE OUTCOMES

- 133 additional cases ascertained for analysis
- 148 risk factor questionnaires have been completed
- 187 tumors analyzed by Dr. Joseph Marcus and Dr. David Page
- 98 additional cases to be added to Drs. Marcus and Page's analysis
- 90 cases have completed ER, PR, and c-erbB-2 testing and yet to be analyzed

CONCLUSIONS & DISCUSSION

Creighton University has one of the largest resource of Hereditary Breast Ovarian Cancer families in the world. As previously reported, Mulcahy and Platt used this resource to identify an excess of medullary carcinomas in 1981 (1). In 1988 (2) we have reported an increased mitotic rate and suggested in 1994, in the preliminary study of this grant, that the proliferative phenotype was due to the BRCA1 subset of breast cancers (3). Other extensive reports on the phenotypes of BRCA1 and BRCA2 (4-6) were subsequently confirmed in additional details by the Breast Cancer Linkage Consortium (7) and other groups.

Due to unforseen staffing conflicts at Baptist Memorial Hospital in St. Louis, Missouri, Dr. Marcus and Dr. Page were unable to meet in order to complete the analysis on the additional 98 cases and add the data to finalize this study. The granted extension of another 12 months to complete this analysis is deeply appreciated. We look forward to the results that the final analysis will show us in regards to the differences in the phenotypes of breast cancer in BRCA1 and BRCA2 genetic mutations. Once more data is collected and analyzed towards the end of this study a complete statistical analysis will be performed on the data set.

Below is a summary of the findings of the analysis completed for last years report (8).

BRCA1 vs BRCA2 Hereditary Breast Cancer

- **Higher grade (nuclear, mitotic, total grades)**

- **More prevalent DNA aneuploidy**
- **Higher proliferation (high DNA aneuploid S phase fraction and mitotic rate)**
- **More medullary group carcinomas (typical and atypical medullary, ductal with medullary features)**
- **More tumor infiltration by mononuclear inflammatory cells**
- **Deficit of ductal and lobular in situ carcinoma**
- **Deficit of tubular-lobular group carcinomas (lobular, tubulolobular, tubular, cribriform, variants)**
- **Decreased expression of estrogen receptor and c-erbB2 oncogene protein**

When compared with non-hereditary breast cancers (4,5) BRCA2 HBCs appear to be more similar to usual breast carcinomas. BRCA1 HBC appears to be the predominantly deviant phenotype.

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Table 1: Status of Eligible Cases

Total Number of Eligible Cases	**530**
Unobtainable permission forms	**142**
No response to invite letter	**68**
Treating hospital unknown	**37**
Lost to contact	**15**
Found to be deceased	**5**
Refused to participate	**4**
Ascertained permission forms	**388**
Hospital did not respond to request	**31**
Slides and blocks no longer available	**72**
Total Number of Ascertained Slides and Blocks	**285**

Table 2: Status of Ascertained Slides and Tissue Blocks

Ascertained Slides and Tissue Blocks	**285**
Completed pathologic analysis	**187**
Completed H&E slides and DNA flow cytometry	**280**
Pending pathologic analysis	**98**
Completed ER, PR, c-erbB-2	**90**